RATIONALPRESCRIBING, UTILIZATIONANDPHARMACOVIGILANCEOFA NTIMICROBIALAGENTSAMONGPATIENTSAD MITTEDINMEDICINEWARDATATERTIARYCAR EHOSPITALOF TRIPURA

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Submitted to

SRI BALAJI VIDYAPEETH

Submitted by

Mrs. Maitrayee Chakraborty

UIN: [1805002002]

Under the Guidance of

Dr.Manimekalai K

Professor and Head, Department of Pharmacology

MGMCRI, Pillaiyarkuppam, Puducherry- 607 402.

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INTRODUCTION

In the developing world, infectious diseases are among the primary cause of death, which is worsened by the emergence of antimicrobial resistance (AMR). In this regard, communities in these areas often exhibit this resistance and that leads to treatment failures as well as an increased utilization of health care[1]. Given these limitations in accessing advanced therapies in developing countries and growing resistance levels, it is worth noting that declining efficacy of combined antimicrobial agents (CMAs) is a major concern.

India for example grapples with significant prevalence of AMA use ranging between 24% and 67%[2]. Consequently, regulatory agencies have introduced measures such as Schedule H1 under the existing Drug and Cosmetics Act, 1945 to curb irrational prescribing practices[3]. Solving these problems necessitates rational drug prescription which means obtaining maximum therapeutic effect with minimal drugs at reasonable costs.Appraising usage trends for medications using WHO indicators becomes critical for promoting rational drug use worldwide[8]. The importance of inappropriate AMA use is highlighted in the 2011 World Medicines Situation report calling for intervention. To monitor outcomes and ensure responsible prescribing, guidelines should be put in place concerning AMA usage.

The rationality of AMA usage is still controversial in modern medical practice. Global rational drug policies are being supported through initiatives like WHO's Action Programme on Essential Drugs[5]. For India, organizations such as Delhi Society for Promotion of Rational Use of Drugs (DSPRUD) promote prudent use of medications. Programs like Antibiotics Smart Use (ASU) introduce creative alternatives against antimicrobial resistance[6].Health centres should establish antibiotic

stewardship programs for ensuring appropriate AMA utilization. Prescribing practice play a vital role in determining therapeutic effectiveness and patient outcomes. Improving patient quality of life requires upgrading medical standards across healthcare delivery systems.

The purpose of studies on prescribing patterns is to assess and modify prescribing practices towards ensuring rational cost-effective drug utilization and control[7].

A significant threat to patients' safety is posed by adverse drug reactions (ADRs) that are defined by the World Health Organization (WHO) as noxious unintended response to a drug occurring at doses typically used for disease treatment[18]. Understanding, recognizing and preventing these adverse drug events (ADEs) fall within the realm of pharmacovigilance which aims at guaranteeing patient's safety[10]..

Indian undergraduate medical curriculum guidelines have included drug safety since 1997 but have not been fully implemented[17]. Another concept in healthcare "prevention is better than cure" has offered an alternative path through which ADRs could be addressed with an aim of reducing instances leading to prolonged hospitalization, low quality life output and poor health condition among persons suffering from various diseases. This is more pronounced in developing countries like India where the cost burden related to ADR-related hospitalizations puts a lot pressure on healthcare systems[9,10].

However, despite the pressing need, India's pharmacovigilance drive is still underdeveloped with monitoring and reporting being in their infancy stage. In contrast

with global average of 5%, Indian pharmacovigilance rate falls below 1% making it abundantly clear that there is a pressing necessity for improvement[9,10].

This study was initiated to evaluate drug utilization patterns, prescription appropriateness and ADRs among patients admitted to medicine ward of a tertiary care hospital in Tripura due to lack of data on antimicrobial agent (AMA) use in Northeastern region of India. The findings of this research will help identify any specific problems and necessary measures for effective pharmacovigilance in this area thereby leading to better strategies for patient safety and medication optimization.

AIMS AND OBJECTIVES

- Evaluate the **drug prescribing patterns of antimicrobial agents** (AMAs) in the medicine ward of a tertiary care hospital.

- Assess the appropriateness of antimicrobial agent in prescriptions in accordance with established guidelines and best practices.

- Investigate the occurrence and **types of adverse drug reactions** (ADRs) associated with the use of antimicrobial agents.

HYPOTHESIS/RESEARCH QUESTION

The purpose of this work is to test whether antimicrobial agents (AMAs) are given to patients hospitalised to a tertiary care hospital in Tripura's medical ward in accordance with accepted standards and best practices?The utilisation, guidelines and limitation policies for antimicrobial agents will be aided by the results of this study in order to rationally prescribe antibiotics to patients.

REVIEW OF LITERATURE

Prescribing and Utilization Pattern of AMAs

The beginning of drug utilization studies can be traced back to the early 1960s. In 1985, WHO convened a major conference in Nairobi on the rational use of Drugs. Since that time there wasincreased efforts to improve drug use practices. WHO prescribing indicators are one of the most widely accepted tools which can be used to assess prescribing pattern in health care facilities. Drug use studies by means of indicators will fall into four broad categories: describing current treatment practices; comparing the performance of individual facilities or prescribers; periodic monitoring & supervision of specific drug use behaviours; assessing the impact of an intervention[6,7].

JubarajSingha et.al have done a study with the aim to evaluate the prescribing and utilization pattern of antibiotic use in the department of medicine for in patients in the tertiary care hospital at Gauhati ensuring rational drug therapy. They have done an observational and prospective study and evaluated the rationality of prescriptions by using the WHO core drug prescribing indicators. The findings of this study revealed that drug utilization pattern were not optimal in accordance with the standard values of WHO prescribing indicators[11].

Appropriateness of prescription of AMAs

Bincy Benjamin et. al planned a prospective, observational study to explore and describe the current pattern of antimicrobial prescribing practices and utilization in critically ill patients. Their study revealed that appropriate use of AMAs and culture sensitivity pattern in ICUs is highly beneficial for the proper functioning of the hospital[12].

Ina Willemsenet. al conducted a study to determine the usefulness of prevalence surveys to measure antimicrobial consumption in the hospital, to determine the appropriateness of AMT and to identify determinants of inappropriate use. The appropriateness of AMT is determined using a standardized method developed by Gyssenset al[13].

Akram Ahmad et. al. conducted cross sectional, prospective observational study to procure information about prescribing patterns of antibiotics on a data collection form in the general medicine ward of tertiary care hospital in South India. This study reveals that there are many standard treatment guidelines available from various state government agencies. Antimicrobial policies given by central government for rational use of antibiotics in the country are not adhered by physicians[3].

Parvathy R Panickeret.alconducted a study to assist the pattern of antimicrobial prescriptions in terms of the prevalence of a variety of antimicrobial uses including frequency, doses and intervals, rate of administration and appropriateness of the choice of antimicrobials. In their study they have found that antimicrobials were prescribed frequently for any infectious disease without identifying the causative organism and assessing the antimicrobial susceptibility in patients[7].

B. Rajalingamet. al conducted a study to analyse the rational use of antibiotics using Micromedex and NFI (National Formulary of India)and to report the irrational use of antibiotics. In their study they have found that in comparison with standard guidelines (Micromedex, NFI) deviations of treatment were observed. The results of this study clearly demonstrate that majority of antibiotics were not complying with the

criteria developed for the assessment of rationality. Hence, they had concluded from the present study that though there is successful combat of infection using antimicrobial agents it is desirable to adopt treatment protocol to increase the success rate[14].

As antimicrobials are the most common drugs, prescribed for several life threatening and trivial infections. It has been observed that 64% of antimicrobial agents prescribed are neither indicated nor appropriate and most of them are without an appropriate bacteriological basis. HenceVelvizhyRandJohan Pandian J had done a prospective observational study to find out the current trends of prescribing fixed dose combination of antimicrobial agents in the post-operative ward of tertiary care teaching hospitalised pretested case record form. They had stated that the prescribers should undergo a continuing medical education (CME) course, once in a year to be aware of the newer drug combinations introduced into the market and their adverse drug reactions, so that the prescribing practices become not only justifiable but evidence-based also[15].

The Medication Appropriateness Index (MAI) was originally developed by Hanlon et. al in 1992 to assist physicians and pharmacists in assessing the appropriateness of medication for given patients. Alam K et. al conducted a study to know the appropriateness of antibiotic therapy in the patients with Enteric Fever using Medication Appropriateness Index criteria. Their finding suggests that more than thirty percent of patients treated for received inappropriate antibiotics[16].

ADRs among AMAs

Following the thalidomide disaster of 1961, when Dr. McBride of Australia reported increased frequency of birth defects (seal limbs) that left 10,000 babies

disabled for life, monitoring centres were started world over. A 1998 report estimated that 1,06,000 Americans die each year because of adverse reactions to prescription medications[17].

According to an estimate of a Swedish study, 3.1% of deaths in the general population (encompassing subjects who died in and outside the hospitals) are due to ADRs. A study revealed the prevalence rate of ADEs among hospitalized patients of England as 3.2%, Germany as 4.8% and the United States of America (USA) as 5.6%.

There is less pharmacovigilance activity, lack of awareness and lack of interest of health care professionals in ADR reporting and documentation. Therefore, PrithulBhattacharjee et.alconducted a retrospective study to identify ADRs and assess their pattern. In their study they have used the reports of ADRs which were recorded as per the standard guidelines fixed by pharmacovigilance programme of India (PvPI). Naranjo ADR probability scale was used to assess the causality of suspected ADRs. Severity of ADRs was identified using modified Hartwig's criteria. Types of ADRs were identified using Rawlins and Thompson classification[18].

Some studies concluded that antibiotics comprise the major volume of the drug familyand in patient prescriptions and thus are the most irrationally prescribed drug class. So, implementation of antibiotic guidelines for the hospital scenario and strict adherence should beensured to promote their rational use.

METHODOLOGY

Study Design: A cross-sectional study.

Study area: Tripura Medical College&Dr. BRAM Teaching Hospital.

Study setting: Medicine inpatient department (IPD) & department of Pharmacology

Study population: Patients admitted in Medicine inpatient department (IPD).

Sample size: 1240 patients

Sample size calculation: The required sample size is calculated from the formula, $N= 4pq/l^2$,

p = 10% (0.1) [assuming antibiotic prescription rate as 50%].

q= (1-p) = 1-0.1=0.9.

l = allowable error (20% of p). 95% confidence interval.

So,the required sample size : $4\times0.1\times0.9/ (0.002)^2 = 900$ (1200 had been taken as the expert members of RAC suggested).

Inclusion criteria: All patients admitted in the department of medicine and receiving AMAs was included in the study.

Study tools: For drug prescribing and utilization pattern prescribing indicators laid down by WHO was used[8].

National treatment guidelines for antimicrobial use in infectious diseases (version 1.0, 2016) by National Centre for Disease Control, Government of India and modified Medication Appropriateness Index (MAI) was used to assess the appropriateness of antimicrobial use[19,16].

ADRs was recorded in the suspected adverse drug reaction reporting form issued by Indian pharmacopeia commission[20].

Study techniques: Study was conducted after obtaining informed written consent from each patient in their own language. Each patient was interviewed individually using a case record form for recording relevant data.

To Assess Prescription Pattern, WHO core prescribing indicators[8] was used with some modifications as per the objectives of the study. The following indicators was adopted for the study.

1. Average number of drugs per encounter
2. Average numberof AMAs prescribed per encounter.
3. Percentage of encounters with an injection of AMAs prescribed
4. Percentage of AMAs prescribed by generic names
5. Percentage of encounter with AMAs prescribed from National List of Essential Medicine, India (NLEM 2015)
6. Percentage of encounter with fixed –dose combination (FDC) of AMAs prescribed
7. Percentage of encounter with fixed –dose combination (FDC) of AMAs prescribedfrom National List of Essential Medicine, India (NLEM 2015)

The choice of AMAs and number of AMAs prescribed empiricallybased on the prevailing pattern of infection and cost effectiveness was identified andany change in empiric therapy after laboratory data was also noted.

To analyze appropriateness: In this study,National treatment guidelines for antimicrobial use in infectious diseases (version 1.0, 2016) by National Centre for

Disease Control, Government of Indiaand modified MAI criteria to assess theappropriatenessof antibiotics therapy[19,16]was used.MAI is a validated and reliability tested instrument and wasused in several studies evaluating appropriateness. In this study, modified MAI criterion which was devised for evaluatingantibiotic prescribing in inpatients was used. It has items which include indication, effectiveness, dosage,duration, direction, drug-drug interactions, drug-diseaseinteractions, practicality, cost and duplication of therapy. Rating was given to each item for each patient as follows:

Item	A	B	C
1. Is there an indication for the antimicrobial? Indication is defined as the sign, symptom, disease orconditionfor whichthemedicationisprescribed.Thisquestionassesses whetherthereissufficientreasonfortheuseofthedrug.Sufficientreasonincludescurative, prophylactic orempiricaltherapyforaninfectiousdisease.	Indicated	Marginal	Not indicated
2. Is the antimicrobial effective for the disease? Effective is defined as producing a beneficial result. The question assesses whether the drug prescribed iscapable of being effective for the indication in a population of patients.	Effective	Marginal	Ineffective

3. Is the dosage correct? It is defined as the total amount of medication administered during period for therapy as per National treatment guidelines for antimicrobial use.	Correct	Marginal	Incorrect
4. Are the orders correct? Orders in this study is defined as the instructions given for the use of a medication where we will assess the route of administration, relationship to food and liquid, the schedule and time of the day.	Correct	Marginal	Incorrect
5. Are the orders practical? It is defined as capable of being used or being put into practice where we will be assessing whether the directions for use were practical for the patient adherence.	Practical	Marginal	Impractical
6. Are there clinically significant drug–drug interactions? It is defined as the effect one medication has on another medicine when administered concomitantly. To assess this we will use Micromedex 2 healthcare series.	Insignificant	Marginal	Significant
7. Are there clinically significant drug–disease interactions?	Insignificant	Marginal	Significant

It is defined as the effect that the medicine has on a pre-existing disease or condition and here we will assess whether the medicine worsened the patient's disease or condition.			
8. Is there unnecessary duplication with other drugs? Unnecessary duplication is defined as use of 2 medicines from the same chemical or pharmacologic class simultaneously in a manner that there is no beneficial effects.	Necessary duplication	Marginal	Unnecessary
9. Is the duration of therapy acceptable? It is defined as the length of therapy. In this study, we will assess the length of therapy that the patient has received according to National treatment guidelines for antimicrobial use.	Acceptable	Marginal	Not acceptable
10. Is this antimicrobial the least expensive alternative compared with others of equal utility? In this we will assess the cost of the drug compared to other agents of equal efficacy and tolerability.	Less expensive	Equally expensive	More expensive

For each A or B rating, the drug receives no score. For a C rating, the drug is assigned a relative weight based on the importance of the item: 3 points for items 1

and 2, 2 points for items 3, 4, 6, and 7, and 1 point for items 5, 8, and 10. Drugs rated as "not indicated" in item 1 are rated as inappropriate (C) for duration and expense (items 9 and 10). Possible values of the summed MAI for a given antimicrobial are integers from 0 (no inappropriate items) to 18 (all items inappropriate).

We were determining only for inpatients the impacts of appropriateness of antibiotic prescribing on patient's recovery status and their days of hospitalization.

To analyse the Pharmacovigilance all the "suspected ADR reporting forms" of Indian Pharmacopoeia Commission (IPC)[20] were filled up by health care professionals in in patient Departments (IPD).For each patient the form was completed with regard to

- Age of the patient,
- Gender of the patient,
- Number of drug(s) prescribed
- Duration of treatment (days).
- Number of ailment(s), the patient was suffering from,
- Causality of the ADR(s),
- Severity of the identified ADR(s),
- Type of ADR(s).

The causality assessment of the ADRs was done using WHO-UMC Causality Categories. The ADRs were categorized as "certain", probable or likely", "possible", "unlikely", "conditional or unclassified" and "unassessable or unclassifiable"[18].

Severity of the identified ADRs was assessed at different levels, ranging between 1 and 7 using modified Hartwig's criteria. Mild ADRs belonged to levels 1

and 2, moderateADRs belonged to level 3 and 4 and severe ADRs were level 5 and above. Types of ADRs were identified usingRawlins and Thompson classification[18].

Ethical approval: Ethical approval has been taken from the Institutional Ethics Committee.

Confidentiality: The study strictly maintained the confidentiality for each individual patient.

RESULTS

Table 1: Association between Age group and No. of AMAs prescribed per encounter (N=1240)

Age group	No. of AMAs prescribed per encounter N (%)					P value
	0	1	2	3	4	
<20 years	5 (7.7)	27 (41.5)	20 (30.8)	13 (20.0)	0 (0)	0.001
21-30 years	4 (5.2)	29 (37.7)	21 (27.3)	16 (20.8)	7 (9.1)	
31-40 years	17 (9.1)	97 (51.9)	51 (27.3)	18 (9.6)	4 (2.1)	
41-50 years	41 (17.2)	99 (41.6)	70 (29.4)	26 (10.9)	2 (0.9)	
51-60 years	50 (17.4)	122 (42.5)	83 (28.9)	24 (8.4)	8 (2.8)	
>60 years	61 (15.8)	200 (51.7)	96 (24.8)	20 (5.2)	10 (2.6)	

Above table shows that higher number of AMAs (i.e. 3 and 4 AMAs) are being used among the younger age group (in patients < 30 years) as compared to patients > 30 years but use of single AMA is more among age group >40 years and these differences are found to be statistically significant with a p value 0.001.

Table 2: Injectable AMAs use in comparison with age group (N=1240)

Age group	Injectable AMAs use N (%)		P value
	Yes	No	
<20 years	55 (84.6)	10 (15.4)	0.02
21-30 years	71 (92.2)	6 (7.8)	
31-40 years	150 (80.2)	37 (19.8)	
41-50 years	181 (76.1)	57 (23.9)	
51-60 years	216 (75.3)	71 (24.7)	
>60 years	307 (79.3)	80 (20.7)	

Above table shows that use of injectable AMAs is more in younger age group (≤30 years) than in patients >50 years. These differences are found to be statistically significant with a p value of 0.02.

Table 3: Association between age group and appropriateness of AMAs use.

Age group	Appropriateness of AMA use			P value
	Appropriate	Inappropriate	Moderately	
<20 years	47 (72.3%)	17 (26.2%)	1 (1.5%)	0.16
21-30 years	56 (72.7%)	20 (26.0%)	1 (1.3%)	
31-40 years	137 (73.3%)	46 (24.6%)	4 (2.1%)	
41-50 years	172 (72.3%)	64 (26.9%)	2 (0.8%)	
51-60 years	223 (77.7%)	62 (21.6%)	2 (0.7%)	
>60 years	306 (79.1%)	70 (18.1%)	11 (2.8%)	

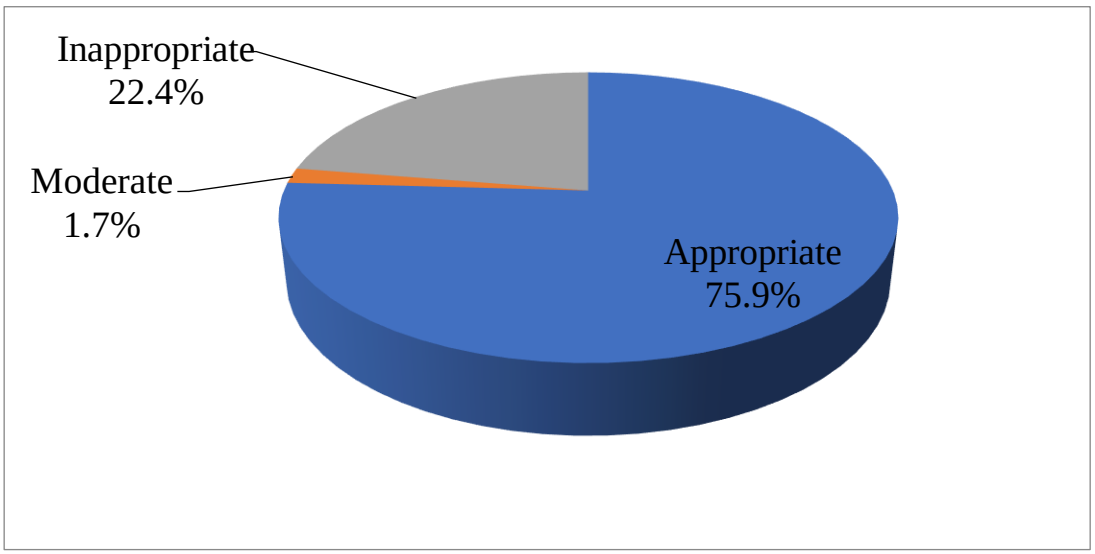
There is no significant difference found in appropriate use of AMAs across the age groups, however the appropriateness of AMA use was highest (79.1% and 77.7%) in patients> 60 years and between 51-60 years respectively than in the younger age groups but it is statistically not significant (p value 0.16).

Table 4: Association between NLEM and appropriateness of AMA use (N=1240)

NLEM	AMA Appropriateness			P value
	Appropriate	Inappropriate	Moderately	
Yes	268 (78.8%)	66 (19.4%)	6 (1.8%)	Not significant
No	673 (74.7%)	213 (23.6%)	15 (1.7%)	

Above table 4 demonstrated that AMAs under NLEM category were more associated with appropriateness of AMA use (78.8%) as compared to non-NLEM AMAs (74.7%) The difference is statistically not significant.

Figure 1:Appropriateness of prescription



Above figure1 demonstrated that 75.9% prescriptions of AMAs showed appropriateness as compared to inappropriateness (22.4%).

Table 5: Relationship between use of injectable AMA use and adverse drug reaction causality.

Encounter injectable AMAs	ADR causality		P value
	Possible	probable/likely	
Yes	418 (42.7%)	562 (57.3%)	0.57
No	117 (44.8%)	144 (55.2%)	

There is no significant association found between ADR causality as possible or probable with injectable AMA use (p value 0.57).

Table 6: Antibiotic class of AMAs with their common indications (N=575)

Antibiotic class / group	N (%)	Common Indication	N (%)
Piperacillin + Tazobactum	280 (48.9%)	Respiratory diseases	81%
Ceftriaxone + Salbactum	112 (19.5%)	Fever, weakness	87%
Cefotaxime + Salbactum	72 (12.5%)	UTI	95%
Cefoperazone + Salbactum	80 (13.9%)	CKD with Hypertension	90%

DISCUSSION

The results of this study offer significant new information about the appropriateness, adverse drug reactions (ADRs) and prescribing practices of antibiotics (AMAs) at Tripura, India, tertiary care facility. The study set out to examine these parameters in order to ascertain whether or not AMAs were given in accordance with recognised norms and best practices.

The results indicate that considerable patterns are noticeable in recommending practice of AMA at various ages. Remarkably, young patients (less than 30 years) were more likely to receive higher number of AMAs per encounter including a larger proportion for injectable AMAS compared with older group. But there were no noticeable changes in age group specific relevance of AMA utilization. It offers a chance to conserve reasonable prescription customs via the intervention as young patients can be more likely to get overmedication or misuse AMAs.

Both the consumption and appropriateness of AMAs listed on NLEM was also evaluated in this study. The findings noted were the likelihood of AMAs that belonged to NLEM than others. This signifies the importance of adhering to major medication lists and rules in prescription filling that would enable, for promoting safe drug use.

With respect to adverse drug reactions, baseline analysis revealed no statistically significant relationship between the use of injectable AMA and causation of ADRs. It follows that the change in mode of administration could not greatly influence or affect a case if it occurred. It also becomes necessary to determine some ADR types and possible connections of these types with many groups among the list; one such research aim can be used for improvement in safety for patients as well as

reduction of hospitalisations associated by various patterns or ADRs cases. Additional research on specific ADR categories and their possible associations to other classes of the abnormal metabolic activity-AMA might be needed nowadays in order to promote patient safety and decrease hospitalisations due to adverse drug reactions.

The study revealed that the most highly prescribed AMA, mainly for respiratory disorders was piperacillin + tazobactum. Other cephalosporin combinations were next prescribed for significant temperatures, UTIs and various other disorders. Ceftriaxone and doxycycline were standard AMAs widely utilized in cases of fever, as well UTIs respectively. These findings, therefore, suggest the urgency for specific measures to mitigate chances of antibiotic resistance, ensure proper choice upon use of drugs and improve prescribing processes.

This research offers a valuable insights into prescription, adequacy and ADR related to the emergence of an adventitious medicine effects in tertiary care hospital Tripura,India. The data obtained in the studies identified spots that rational prescribing practices is required to be strengthened on so as to increase effectiveness of treatment and enhance safety for patients. These are areas of equipoise and thus need strict compliance to essential medication lists, limited AMAs use in these settings coupled with monitoring for adverse drug reactions. More research and precisely directed therapies based on these findings could prevent the worsening problem of antibiotic resistance and enhance service delivery in such environments towards a better quality.

SUMMARY AND CONCLUSION

In conclusion, this study provides relevant comprehension regarding prescription patterns along with the suitability of antimicrobial agent prescribing and adverse drug reactions (ADRs) observed in an AMA among patients visiting a Tertiary Care Hospital located within state(Tripura). It focuses on the importance of following national treatment recommendations and proper utilisation of AMA mainly in young patients. Future attempts should mainly involve directed initiatives containing efforts aimed at boosting prescribers' behaviour through medical personnel training programs and antibiotic stewardship initiatives. Another aspect which is vital to understand includes the strengthening of pharmacovigilance initiatives that allow monitoring and minimizing ADRs related to AMA. Observing wise prescription techniques and pharmacovigilance can therefore contain the spread of antibiotic resistance while enhancing treatment outcomes in the region.

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